

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MCCALLUM, W.
CRUIKSHANK & FAIRWEATHER
19 Royal Exchange Square
Glasgow G1 3AE
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year) 03.10.2001

Applicant's or agent's file reference
PC/DM/P10959PC

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/03444

International filing date (day/month/year)
06/09/2000

Priority date (day/month/year)
07/09/1999

Applicant
THE UNIVERSITY COURT OF THE UNIVERSITY OF GLASGOW

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

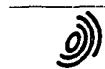
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
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Authorized officer

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PCT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 14 May 2001 (14.05.01)	Applicant's or agent's file reference MGH/PC/P10959PC
International application No. PCT/GB00/03444	Priority date (day/month/year) 07 September 1999 (07.09.99)
International filing date (day/month/year) 06 September 2000 (06.09.00)	
Applicant DAVIES, Roger, Wayne et al	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

23 March 2001 (23.03.01)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38



REC'D 03 OCT 2001

WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC/DM/P10959PC		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) FOR FURTHER ACTION
International application No. PCT/GB00/03444	International filing date (day/month/year) 06/09/2000	Priority date (day/month/year) 07/09/1999
International Patent Classification (IPC) or national classification and IPC G01N33/68		
Applicant THE UNIVERSITY COURT OF THE UNIVERSITY OF GLASGOW		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 10 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input checked="" type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input checked="" type="checkbox"/> Certain observations on the international application</p>		
Date of submission of the demand 23/03/2001		Date of completion of this report 03.10.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized officer Hoekstra, S Telephone No. +31 70 340 2847 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/03444

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-103 as originally filed

Claims, No.:

1-36 as originally filed

Sequence listing part of the description, pages:

1/586 - 586/586, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/03444

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 2,7-17, 19-21, 23-35.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 7-17, 19-21 are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 2,7-17, 19-21, 23-35 entirely and 1, 3-6, 18, 22 and 36 in aprt.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/03444

- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
- ☐ all parts.
- ☒ the parts relating to claims Nos. 1, 3-6, 18, 22, 36.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims
	No:	Claims 1, 3-6, 18, 22, 36
Inventive step (IS)	Yes:	Claims
	No:	Claims 1, 3-6, 18, 22, 36
Industrial applicability (IA)	Yes:	Claims 1, 3-6, 18, 22, 36
	No:	Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

This written opinion and the final preliminary examination report is limited to claims 1,3-6, 18, 22 and 36 insofar as they are limited to SEQ ID No.1

No international search report has been drawn up for the other 901 inventions or for subject-matter under Article 17(2)b PCT (Rule 66.1(e) PCT) and no opinion on those inventions or subject-matter is derivable from this preliminary examination report.

Claims 7-17, 19-21 relate to an extremely large number of possible compounds. In fact, the claims contain so many options that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises.

Moreover, these compounds are defined by reference to a desirable characteristic or property, namely that they can be identified by the method of the screening assay claims.

These claims cover all compounds having this characteristic or property, whereas the application provides no support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for such compounds. In the present case, the claims lack support, and the application lacks disclosure. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Consequently, no meaningful preliminary examination be executed for these claims.

In addition it is noted that these claims can also not define the subject-matter for which protection can be sought (Article 6 PCT, first sentence). It is highly likely that any known pesticide e.g. those listed in "The pesticide manual" (ISBN 0 948404 79 5) falls within the scope of claim 7. The claims do not allow any discrimination between known and novel subject-matter and the skilled person will always be in doubt if his compound falls under the claim or not.

Re Item IV

Lack of unity of invention

The IPEA agrees with the ISA that this international application relates to 902 separate inventions in the sense of Article 3(4)(iii) and Rule 13 PCT. The International Search Report only covers the first invention, pursuant to rule 66.1(e) PCT this IPER is limited to the preliminary examination of this first invention only.

Invention 1: claims 1-6, 18, 22, 36 in part

Screening assay, method for identifying or producing compounds having a potentially pesticidal activity, comprising a sequence selected from SEQ ID No. 1 (Frizzled gene) specific fragments thereof, homologues thereof, or the encoded proteins thereof.

Inventions 2-783: claims 1-6, 18, 22, 36 in part

As for invention 1, each invention 2-544 comprising one SEQ ID. selected from SEQ. ID. No. 2-429 and 784-898.

Inventions 784-902: Claims 1-6, 18, 22-36 in part

As for invention 1, each invention 545-902 comprising one SEQ ID. selected from SEQ ID's 430-783 and 899-902 as well as the corresponding isolated polynucleotide fragment per se.

A PCT application shall comply with the requirement of unity of invention (Article 3(4)(iii) PCT). Rule 13.1 prescribes this requirement as being fulfilled if the application relates to one invention only. If the application relates to more than one invention, as is presently the case, then they must be so linked as to form a single general inventive concept. Such a link is, in view of the state of the art, not present. In consequence the application is considered to relate to at least 902 separate inventions of which the one first mentioned in the claims has been searched. The application as a whole sets out to solve the problem of identifying essential genes of an organism in order to predict

pesticide targets, drug target, herbicide targets etc. The definition of a gene being essential has been arbitrarily determined by the applicant so as to include "semi-lethal" mutations. An example solution to this problem with respect to *Drosophila* as presented by the present application (not claimed) is to mutagenise *drosophila* by P-element insertions and to select lethal and semi-lethal mutants which are subsequently characterised by cloning and sequencing DNA surrounding the P-elements. This results in DNA sequences similar, or identical, to known sequences as well as DNA sequences to yet unknown genes. The application further proposes to solve the problem of identifying further essential genes of other organisms, which are not yet known per se, by comparing a gene with the so identified allegedly novel sequences (Claims 26-28). The single general concept linking all claimed inventions is that identification of essential genes of an organism leads to the identification of drug targets, pesticide targets, herbicide targets etc. It is common knowledge in e.g. the pesticide field that many, if not all, pesticides provide a certain biochemical activity. If this activity affects an essential function of the organism it will die or it will be more vulnerable to its environment or to disease or attack. The formulation of this concept follows logically from common knowledge in the field of e.g. pesticides. This single general concept can hence not be the single general inventive concept of Rule 13.1 PCT. The closest prior art at hand is either of WO97/39357 (p. 10, l. 30 -p-12, l. 25), US5871940 (col. 2, l.20-22) or US574336 (col. 5, l. 22-28; col. 6, l. 27-31) WO97/39357 disclosed the binding relation between Wnt and the Wnt receptor (= Dfz2 = frizzled gene; cf p. 7, lines 1-4). A screening for drug candidates is done by expressing the essential gene Dfz2 on the surface of cells and monitoring modulation of interaction between Wnt and the receptor. It is noted that the "frizzled gene" gene has been identified in the description by matching with one of the 902 sequences (SEQ ID No. 1). US5871940 disclosed the tipE mutant gene of *drosophila melanogaster* as a gene which mutation leads to the semi lethal condition of paralysis at temperature above 38°. The DNA sequence of the gene has been disclosed as well as a method of identifying agents which modulate the physiological activity of the translated gene product using the gene. It is noted that the tipE gene has been identified in the description by matching with one of the 902 sequences (SEQ ID No. 39). Also US5747336 (05.05.99) disclosed an essential gene and proposed it as a target for drug screening (human muscarinic acetylcholine esterase receptor). It is noted that the muscarinic acetylcholinic receptor has been identified in the description by matching with one of the 902 sequences (SEQ ID No. 3). Because no common technical effect has been linked with a structural feature

present in all 902 SEQ. ID's, or in the so identified essential genes, the broadest possible problem to be solved is to provide further DNA sequences derived from essential genes serving as possible targets for drug screening pesticide screening, herbicide screening etc. The solutions proposed thereto are the separate sequences 1-902. If these sequences would be linked so as to form a single general inventive concept than the condition of Rule 13.2 must be met, i.e. there must be a same or corresponding special technical feature shared by all 902 SEQ ID's or in the so identified essential genes, which makes up the contribution to the state of the art. Neither the claims nor the list of sequences or the application as a whole discloses a technical feature or a technical effect linked thereto which is the same for all 902 inventions and which makes up a contribution over the state of the art (i.e. over US5871940). A suggested link is the status of the sequences as relating to essential genes which are possible drug targets, pesticide targets etc. But such link constitutes merely a reformulation of the problem to be solved: "To identify essential genes of an organisms to select drug targets, pesticide targets etc." This problem is an obvious desideratum which, as such, cannot make up a contribution over the state of the art, if any. A further suggested link is the fact that these sequences can be used to formulate the assay of claim 1. It is evident, however, that the method features of the assay in claim 1 are generalizations of all technical features of the state of the art assays mentioned in the description. It is immediately clear that the assays used in the description are state of the art assays and can hence not be considered to contribute to a same or corresponding special technical feature making up a contribution over the state of the art (See page 46, last paragraph, page 49, first paragraph etc.). This leaves as only technical feature(s) structural features of the separate SEQ. ID's in claim 1. It is noted that the reason for a gene being essential lies in the uniqueness of the combined features of the gene. Essentiality cannot be considered as a true technical effect of the individual features of a sequences. The "effect" of being essential cannot be derived from a technical effect attributable to any same or corresponding features which a gene shares with other genes. If there are technical features of a gene which it shares, by way of the same or corresponding structural features, with 901 other genes then this feature alone can never render a gene essential. The requirement of unity of invention is not met and each single SEQ ID together with its use has to be evaluated separately against the state of the art for being novel and inventive. And it follows from the above reasoning that the possible non-obviousness of one of the 902 SEQ ID's cannot render the other 901 inventive.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

This statement has been drawn up for subject-matter of claims 1, 3-6, 18, 22 and 36 in as far as it relates to the use of a sequence selected from the group of SEQ. ID No. 1, specific fragments thereof, or homologue thereof.

The first invention of claim 1 reads:

"A screening assay for identifying compounds which have a physiological effect on an organism, the assay comprising the steps of:

- a) reacting a test compound with a protein encoded by an essential gene comprising a sequence selected from the group of SEQ. ID No. 1, specific fragments thereof, or homologue thereof, from the organism; and
- b) detecting any modulatory effect the compound has on the protein."

The application does not meet the requirements of Article 33(2) PCT because claims 1, 3-6, 18, 22 and 36 are not novel over EP882793, page 12, line 44 - page 13; line 52 and claims 16-19 or over EP879881, page 10, line 55 - page 11, line 47.

Moreover, claim 44 of WO9813493 and the parts of its description supporting this claim disclose a more specific screening assay having all features of claims 1,3 and 18.

Claims 1,3 and 18 are also not novel over WO97/3957 page 10, line 30 - page 12, line 25.

In as far as dependent claims could rely on technical features not present in either of the above 4 documents the subject-matter of these claims are considered to relate to subject-matter that follows in an obvious manner from any of these documents taken alone. In fact the notion that screening for compounds interacting in a physiological meaningful manner with the "frizzled" gene product of an organism leads to identification of compounds having a physiological meaningful effect on that organism cannot be the basis for an inventive step as this is known from or rendered obvious by any of the cited screening assays.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/03444

Re Item VIII

Certain observations on the international application

Dependent claims relating to a "functional activity assay" (Claims 5 and 6) are meaningless in the absence of the mentioning of the physiological function of the "frizzled " gene product. Claims 5 and 6 thus render the set of claim unclear contrary to the requirements of Article 6 PCT.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference

(if desired) (12 characters maximum) MGH/PC/P10959PC

Box No. I TITLE OF INVENTION

"ESSENTIAL GENES AND ASSAYS RELATING THERETO"

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

THE UNIVERSITY COURT OF THE UNIVERSITY OF
GLASGOW
Gilbert Scott Building
University Avenue
Glasgow G12 8QQ
United Kingdom

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State (that is, country) of nationality:
GB

State (that is, country) of residence:
GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

DAVIES ROGER WAYNE
University of Glasgow
IBLS Division of Molecular Genetics
Anderson College, 56 Dumbarton Road
Glasgow G11 6NU, United Kingdom

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
GB

State (that is, country) of residence:
GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE: OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address:

McCALLUM, William Potter; MacDOUGALL, Donald Carmichael; SZCZUKA, Jan Tymoteusz; NAISMITH, Robert Stewart; HORNER, Martin Grenville, SHANKS, Andrew; NEWELL, Campbell; KERR, Sheila Agnes Fife; MORELAND, David; GODWIN, Edgar James;
CRUIKSHANK & FAIRWEATHER, 19 ROYAL EXCHANGE SQUARE,
GLASGOW G1 3AE, UNITED KINGDOM (GB)

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0141 221 576

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☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III. FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KAISER KIM
University of Glasgow
IBLS Division of Molecular Genetics
Anderson College, 56 Dumbarton Road
Glasgow G11 6NU, United Kingdom

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

GB

State (that is, country) of residence:

GB

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

YANG MING YAO
University of Cambridge
Department of Genetics
Downing Street
Cambridge
United Kingdom

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

CHINESE

State (that is, country) of residence:

GB

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box N . V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|---|---|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LC Saint Lucia |
| <input checked="" type="checkbox"/> AG Antigua and Barbuda | <input checked="" type="checkbox"/> LK Sri Lanka |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MA Morocco |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BZ Belize | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> MZ Mozambique |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PL Poland |
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| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DM Dominica | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> DZ Algeria | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> ZA South Africa |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | |
| <input checked="" type="checkbox"/> KR Republic of Korea | |
| <input checked="" type="checkbox"/> KZ Kazakhstan | |

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:



Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 07/09/1999	GB9921009.8	UNITED KINGDOM		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):	Request to use results of earlier search; reference to that search (if any earlier search has been carried out by or requested from the International Searching Authority):
ISA /	Date (day/month/year) Number Country (or regional Office)


Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:	This international application is accompanied by the item(s) marked below:
request : 4	1. <input checked="" type="checkbox"/> fee-calculation sheet
description (excluding sequence listing part) : 103	2. <input type="checkbox"/> separate signed power of attorney
claims : 6	3. <input type="checkbox"/> copy of general power of attorney; reference number, if any:
abstract : 1	4. <input type="checkbox"/> statement explaining lack of signature
drawings : 586	5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s):
sequence listing part of description :	6. <input type="checkbox"/> translation of international application into (language):
Total number of sheets : 700	7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material
	8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form
	9. <input checked="" type="checkbox"/> other (specify): Form 23/77

Figure of the drawings which should accompany the abstract:	Language of filing of the international application:
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Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).


MARTIN G. HORNER.

For receiving Office use only		2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
1. Date of actual receipt of the purported international application:		
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.	

For International Bureau use only
Date of receipt of the record copy by the International Bureau: